# (DRAFT FOR REVIEW DO NOT CITE OR QUOTE)

PHARMACOKINETIC PARAMETERS. Dale Hattis, Ph. D., Clark University

This is another of those presentations from the dim, dark ages of the 20th century.

## Newborns, Older Children, and Adults-- Comparisons of Pharmacokinetics and Pharmacokinetic Variability

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**EPA/State of Connecticut Cooperative Agreement, Dr. Bob Sonawane, EPA Project Monitor**

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## Outline

**Objectives for Pharmacokinetic Comparisons**

- **What Information Would We Like to Have to Improve Risk Assessments?**
- **What Kinds of Data are Readily Available?**
- **How Can the Data Be Summarized and Analyzed to Make it More Useful?**

**Description of the Data Collected To Date**

**Analysis of the Group Mean Data**

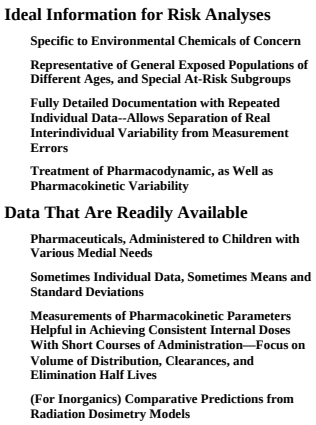
**Variability Among Chemicals in Group Mean Pharmacokinetic Parameters for Young Children vs Adults**

**Pharmacokinetic Interindividual Variability Among Young Children Compared with Variability Among Adults**

I'm going to talk to you first about the goals for these pharmacokinetic comparisons, if only to give you some caveats about what we're doing, what we'd like to have ideally for risk assessment, and how the two are different. Also how we're trying with some bit of consolidation and analysis to bridge some of the gaps between what we'd really like to have and what we actually can lay our hands on. Then I'm going to talk to you about the data that we've collected so far, and our analysis of group mean data from kids of various ages for the set of drugs for which we have data. Then I'll talk to you about the chemical-to-chemical variability in the pharmacokinetic parameters for each of those chemicals from the group mean result for each age group. And, finally I'll talk a bit about the pharmacokinetic interindividual variability within chemicals.

So, basically there are three different levels of variability that we'll be talking about here: Variability from age group to age group for the typical chemical, variability among chemicals, and then variability among individuals within a chemical. Each of those contributes to the overall variability that you would want to analyze as part of assessing the dosimetry that individuals would be likely to get internally.

Now all of this is pharmacokinetics, and as I think you've probably gleaned from the last couple of days, a lot of the real action in this field is likely to be pharmacodynamics. Nevertheless, kids do have some differences from adults pharmacokinetically and, moreover, we have some actual quantitative information about that.




The ideal information that we would like to have for risk analysis would be specific to individual environmental chemicals of concern, representative of the general exposed population, and fully detailed in terms of the documentation with repeated individual data to allow us to separate real interindividual variability from measurement errors. We would also, of course, like to treat the pharmacodynamic as well as the pharmacokinetic variability.

The data that are available are for pharmaceuticals, which are not exactly the same thing as the environmental pollutants of concern, but we're going to take the liberty of saying we don't know how different they are so we'll assume that they're not so different. These pharmaceuticals (drugs) are administered to children, not representative children but children with various medical needs. Sometimes the kids are sick -sometimes quite sick,

and sometimes they're only undergoing a small surgical operation; nevertheless, they have medical needs and, therefore, there could well be some selection bias and some unusual behavior relative to a general population.

Sometimes we have individual data available in the literature reports. Much more frequently we have group mean data and some measure of dispersion like a standard deviation. Which, if they also tell us the sample size (N) we can use to calculate a standard error. But this latter type of information is not ideal. We also have measurements of pharmacokinetic parameters that are helpful in achieving consistent internal doses with short time courses of administration. That's what the original investigators hoped to do; they hoped to make generally short courses of administration. We have some chronic administration data but not too much. And, of course, you can't really have chronic administration data for less than one-week-old newborns; you've just basically got the one shot at it.

For inorganic chemicals we also have available some comparative predictions from models, radiation dosimetry models developed by the International Committee on Radiation Protection (ICRP). And I'm not sure I'm going to get to talk to you about those, but, nevertheless, that's another source of initial comparative information that can be used in the short-run.

**Improving the Usefulness of Available Data with Analysis**

**Assemble and Consolidate Data in a Consistent Form for Analysis**

**Characterize Central Tendencies by Age Group**

**Assess the Magnitude of Differences Among Chemicals in Age-Specific Changes in Pharmacokinetics**

**Assess Whether Differences Among Chemicals in Age-Specific Central Tendencies Are Associated with Mechanistic Categorizations (e.g. Mode of Elimination) that Could Be Used for Predictions for Environmental Chemicals**

**Assess Changes in the Form and Extent of Individual Subject Differences by Age Group**

To improve the usefulness of the available information what we want to do is to first assemble the data in a consistent form. Then we can analyze it and characterize at least the central tendencies of these parameters, mostly volumes of distribution, clearances and elimination half-lives, by age group. Then the idea is to assess the magnitude of differences among chemicals in age-specific changes in pharmacokinetics, and assess whether there are differences among chemicals, classes that are associated with mechanistic categories, categories mainly of the ways in which the chemicals are eliminated from the body. That's how we're hoping, to some extent, to bridge the gap from the drugs to the environmental chemicals. You could conceivably know how the environmental chemical might be eliminated and then make predictions of child metabolic parameters for specific chemicals on the basis of the experience with drugs that are eliminated more or less the same way. Then one could assess changes in the form and extent of interindividual subject differences by age group. Are the kids more variable than the adults? We should be able to assess that.

I'm not going to present too much in the way of conclusions from that analysis because it basically hasn't yet been done. But, my summary first impression from the available data is that often you do have somewhat larger amounts of variability for the youngest child age groups than you find typically for adults.

Table 1

**Table 1**
**Section of the Summary Means Data Base**

| Chemical | Metabolic Type | Parameter | Units | Mean | Std Error | N | Age Range | Mean Age (yrs) | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Alfentanil | CYP3A4 | Cl | ml/min-kg | 1.79 | 0.55 | 11 | premature neonates | =.01 | Jacqz-Aigrain and Burtin, 1996 |
| Alfentanil | CYP3A4 | Cl | ml/min-kg | 2.78 | 0.45 | 18 | full term neonates | =.01 | Jacqz-Aigrain and Burtin, 1996 |
| Alfentanil | CYP3A4 | Cl | ml/min-kg | 4.73 | 0.62 | 8 | 4 to 8 | 5.4 | Meistelman, 1987 |
| Alfentanil | CYP3A4 | Cl | ml/min-kg | 4.20 | 0.78 | 5 | Adult | 20+ | Meistelman, 1987 |
| | | | | | | | | | |
| Alfentanil | CYP3A4 | T1/2 | min | 492 | 72 | 11 | premature neonates | =.01 | Jacqz-Aigrain and Burtin, 1996 |
| Alfentanil | CYP3A4 | T1/2 | min | 269 | 32 | 18 | full term neonates | =.01 | Jacqz-Aigrain and Burtin, 1996 |
| Alfentanil | CYP3A4 | T1/2 | min | 40 | 3 | 8 | 4 to 8 | 5.4 | Meistelman, 1987 |
| Alfentanil | CYP3A4 | T1/2 | min | 97 | 10 | 5 | Adult | 20+ | Meistelman, 1987 |
| Alfentanil | CYP3A4 | T1/2 | min | 114 | 8 | 5 | Adult | 20+ | Lemmens, 1994 |
| **Alfentanil** | **CYP3A4** | **T1/2** | **min** | **105** | **6** | **10** | **Combined Adult** | | |
| | | | | | | | | | |
| Alfentanil | CYP3A4 | Vd | ml/kg | 909 | 135 | 11 | premature neonates | =.01 | Jacqz-Aigrain and Burtin, 1996 |
| Alfentanil | CYP3A4 | Vd | ml/kg | 583 | 55 | 18 | full term neonates | =.01 | Jacqz-Aigrain and Burtin, 1996 |
| Alfentanil | CYP3A4 | Vd | ml/kg | 164 | 39 | 8 | 4 to 8 | 5.4 | Meistelman, 1987 |
| Alfentanil | CYP3A4 | Vd | ml/kg | 458 | 72 | 5 | Adult | 20+ | Meistelman, 1987 |
| Alfentanil | CYP3A4 | Vd | ml/kg | 294 | 17 | 5 | Adult | 20+ | Lemmens, 1994 |
| **Alfentanil** | **CYP3A4** | **Vd** | **ml/kg** | **376** | **37** | **10** | **Combined Adult** | | |

shown a section of the summary means database. This is for one chemical, alfentanil. The first four lines are clearances where we've put the values in the same units (ml/min-kg), and what you see in the next two columns are the means and standard errors. These are for different age groups, pre-term neonates, full-term neonates, four-to-eight-year olds and adults. Other columns provide the number of subjects studied, their mean age, and the reference. And you see in the "means" column, the pattern of rather less clearance for the youngest age groups (neonates) and approaching the adult value for children 4-8 years old.

Similarly, for the half-lives in min, you see the longest half-life in the premature neonates and full-term neonates. You see a rather shorter half-life in the intermediate age group,

lengthening out to a longer half-life in the adult data set. So in all cases I've combined the adult data sets statistically to get a combined result of alfentanil half-life. Although I haven't always combined the children's databases, sometimes I have combined them within narrow-enough age groups.

I'm now going to describe the database that we've assembled so far. We've been working at this not quite a year, so it's time to put up the results that we've got to date. This is not finished, we hope to expand the database further. I've divided these data more or less arbitrarily into the following age categories for the initial analysis

**Table 2**
**Age Groups Represented in the Means Database**

| | Data Groups |
|---|---|
| Premature Neonates (=1 wk) | 11 |
| Full Term Neonates (=1 wk) | 23 |
| Newborns 1 wk- 2 months | 51 |
| Early infants 2-6 months | 23 |
| Crawlers & Toddlers (6 months -2 yrs) | 23 |
| Pre-Adolescents (2-12 years) | 55 |
| Adolescents (12-18 years) | 7 |
| Adults | 69 |
| Total | 262 |

premature neonates, full-term neonates, (both of these less than a week in postnatal age, if the premature neonate is a month old I counted it as no longer premature, although there could well be differences); newborns a week to two months, two to six months, six months to two years, and then pre-adolescent (2-12 yr) and adolescent (12-18 yr). I don't have that much in the way of adolescent data. Nevertheless, it's a large enough database to look at, 260-odd data groups after the consolidation of the adult data for each chemical.

**Table 3**
**Parameters, Chemicals and Subjects in the Means Database**

| | Data Groups | Chemicals | Total Subjects |
|---|---|---|---|
| **AUC** | **14** | **5** | **108** |
| **Clearance** | **77** | **22** | **1944** |
| **Cmax** | **4** | **2** | **30** |
| **T1/2** | **103** | **32** | **1429** |
| **Vd** | **64** | **19** | **803** |
| **Full database** | **262** | **35** | **4314** |

Table 3 lists the distribution of the database by parameters. AUC is the integrated blood concentration times time, with 14 data groups on five chemicals with a total of 108 subjects. These are good data but I don't have enough of them yet to analyze. I mostly have data on total clearance (basically the milliliter-per-kilogram minute, of the central compartment that's cleared from the body), the half-life in units of hours or minutes, and volume of distribution. The full database is 262 data groups with about 35 chemicals.

**Table 4**
**Chemicals (Drugs) Represented**

| | |
|---|---|
| **Alfentanil** | **Midazolam** |
| **Amobarbital** | **Morphine** |
| **Ampicillin** | **Nifedipine** |
| **Antipyrene** | **Oxazepam** |
| **Bromsulphalein** | **Paracetamol (acetaminophen)** |
| **Busulfan** | **Piperacillin** |
| **Bupivacaine** | **Quinidine** |
| **Caffeine** | **Remifentanil** |
| **Cimetidine** | **Teniposide** |
| **Clavulanic Acid** | **Theophylline** |
| **Fentanyl** | **Ticarcillin** |
| **Furosemide** | **Tobramycin** |
| **Gentamicin** | **Tolbutamide** |
| **Ketamine** | **Triazolam** |
| **Lignocaine** | **Valproic Acid** |
| **Lorazepam** | **Vancomycin** |
| **Mepivicaine** | **Zidovudine** |
| **Metoclopramide** | |

Table 4 lists the chemicals that we have some information about. As you see, they're virtually all drugs. In future work it would be desirable to add a few chemicals from the group of environmental chemicals for which we hope to predict pharmacokinetic parameters. Maybe we'll be able to get data on nicotine. However, we probably won't get sufficient data on other important environmental pollutants, e.g., trichloroethylene (TCE).There're just not many exposure experiments where kids' exposures to things like TCE have been monitored and pharmacokinetic parameters calculated. If you did the experiment, not by increasing kids' exposure but by decreasing their normal ambient exposure, it's possible you could get such a design through an institutional review board (IRB).

We've classified each of the chemicals as best we can by the predominant modes of elimination, as illustrated in

**Predominant Modes of Elimination Represented in the Means Database**

| | Data Groups |
|---|---|
| **Renal** | **56** |
| **P450 any** | **134** |
| **CYP3A** | **52** |
| **CYP1A2** | **52** |
| **P450 other than 3A or 1A2** | **30** |
| **Glucuronidation and Sulfation** | **53** |
| **Unclassified** | **19** |

Table 5. About 56 of the data groups had renal elimination as the predominant mode of elimination. Some 134 had cytochrome P450 (CYP) type elimination, that includes 52 with CYP3A, 52 with CYP1A2 and 30 with a CYP form other than 3A or 1A2. The other predominant mode of elimination was glucuronidation and sulfation. Nineteen data groups were unclassified.

The basic technique to bring all of these data together so that they can reinforce each other and tell us something in general for an unknown chemical is to model the log of the mean of each of these parameters as a function of variables representing each chemical and each age group

**Table 6**
**Multiple Regression Analysis for the Means Database**

**For Data Groups Within Each Parameter:**

**Log(Mean) = $B_1$*(1 or 0 for chemical 1) + $B_2$*(1 or 0 for chemical 2) + …**
**+ $B_a$*(1 or 0 for age group 1)**
**+ $B_b$*(1 or 0 for age group 2) + …**

**Chemical-specific "B's" correct for differences among chemicals in average clearance relative to a specific reference chemical (e.g., theophylline)**

**Age-group-specific "B's" assess the average log differences between each age group and the reference group (adults).**

Each of these Bs shown in the basic regression equation ($B_1$, $B_2$) are dummy variables. That is, it is assigned a one if the chemical is that chemical, and zero if it's some other chemical. So $B_1$ might be the indicator for caffeine and $B_2$ might be the indicator for amobarbital. Then there's also another set of dummy variables in the regression for the different age groups ($B_a$, $B_b$). So if the data group was premature infants then this $B_a$ would be one, otherwise it would be zero. In all cases you have to define a reference category for these dummy variables. For most of the analyses, the reference chemical was theophylline, and in all cases the reference age group was adults.

Basically what this provides is the average value of the parameter by chemical and an expectation for the log difference between the half-life or other parameter you're studying for specific age groups relative to the corresponding values for adults.

Essentially, what we're trying to solve for is the typical difference between adults and each of a series of age groups in multiplicative form. That's the virtue of the logarithms, you get your results out in multiplicative differences. We explored three kinds of weighting schemes to see if they made any difference in our analysis

**Table 7**

**Weighting Options Explored**

**Equal weight for each data group**

**Weight Equal to the Square Root of N**
**(some imputations needed when N not given)**

**Weight Equal to the Inverse of the Square of the Ratio of the Standard Error to the Mean (additional imputations needed when either N or standard deviation was not given)**

The first and simplest is just to treat each data group, regardless of how big it is or, what the standard errors are, as equal to every other (i.e. equal weight). The second option is to trust the sample size (Ns) that the authors report but not the standard deviation, because of the uncertainties in determining standard deviations in small groups of data. In this case the weight will be the square root of N.

The third option is to use both the Ns and the standard deviations reported by the original authors to derive a standard error for each mean value in the data base and then take the inverse of the square of that ratio of the standard error to the mean , for the weighting purposes (inverse variance weighting). That's probably the best a priori option. But we wanted to make sure that things wouldn't be vastly different if the analysis were done using other weighting options.

Table 8

**Table 8**
**Example of the Full Regression Results from One Run**

**Dependent Variable—Log(Mean Clearance)**

**Weighting—Equal Weights for Each Datagroup**

| | |
|---|---|
| RSquare | 0.949 |
| Root Mean Square Error | 0.187 |
| Mean of Response | 0.390 |
| Observations (or Sum Wgts) | 77 |

**Parameter Estimates**

| Term | | Estimate | Std Error | t Ratio | Prob>\|t\| |
|---|---|---|---|---|---|
| Intercept | | -0.01 | 0.07 | -0.19 | 0.8497 |
| Alfentanil | | 0.73 | 0.11 | 6.57 | <.0001 |
| Antipyrene | | -0.11 | 0.15 | -0.72 | 0.4732 |
| Bromsulphalein | | 0.97 | 0.09 | 10.28 | <.0001 |
| Bupivacaine | | 0.87 | 0.12 | 7.12 | <.0001 |
| Caffeine | | -0.20 | 0.13 | -1.6 | 0.1151 |
| Clavulanic Acid | | 0.60 | 0.12 | 4.86 | <.0001 |
| Fentanyl | | 1.22 | 0.11 | 11.29 | <.0001 |
| Furosemide | | 0.12 | 0.12 | 1 | 0.3244 |
| Gentamicin | | 0.16 | 0.15 | 1.11 | 0.2708 |
| Ketamine | | 1.35 | 0.11 | 12.52 | <.0001 |
| Lignocaine | | 1.13 | 0.15 | 7.71 | <.0001 |
| Lorazepam | | -0.08 | 0.15 | -0.55 | 0.5822 |
| Midazolam | | 0.86 | 0.15 | 5.93 | <.0001 |
| Morphine | | 1.21 | 0.09 | 12.95 | <.0001 |
| Paracetamol (ac | | -0.41 | 0.15 | -2.73 | 0.0089 |
| Quinidine | | 0.82 | 0.15 | 5.33 | <.0001 |
| Remifentanil | | 1.65 | 0.15 | 11.35 | <.0001 |
| Teniposide | | -0.24 | 0.13 | -1.86 | 0.0697 |
| Ticarcillin | | 0.33 | 0.12 | 2.65 | 0.0107 |
| Valproic Acid | | -0.45 | 0.13 | -3.52 | 0.001 |
| Vancomycin | Antilog | 0.07 | 0.15 | 0.46 | 0.6462 |
| Premature Neona | 0.26 | -0.59 | 0.11 | -5.17 | <.0001 |
| Full Term Neona | 0.41 | -0.39 | 0.10 | -3.85 | 0.0003 |
| 1 wk- 2 months | 0.55 | -0.26 | 0.07 | -3.6 | 0.0008 |
| 2-6 months | 0.95 | -0.02 | 0.09 | -0.23 | 0.82 |
| Crawlers & Todd | 1.45 | 0.16 | 0.09 | 1.73 | 0.09 |
| Pre-Adolescents | 1.28 | 0.11 | 0.07 | 1.45 | 0.15 |
| Adolescents (12 | 0.77 | -0.12 | 0.13 | -0.9 | 0.37 |

gives one example of the full results we obtained from a particular regression run. The numbers opposite the drug names under the “estimate” column are the regression estimates for the dummy variables for the chemicals that were available for the mean clearance parameter. These results were obtained using the simplest weighting scheme with equal weights for each data group.

At the bottom of the table are the regression estimates for the various age groups. These numbers are the log estimates of the how different are the different age groups from adults. A log difference of - 0.59 means that on average the premature neonates have only $10^{-0.59}$ = 26% of the clearance of adults. Similarly, the - 0.39 means that the full-term neonates on average had about 40% of the clearance of the adults, and so on. So the bottom line here is that the premature neonates, the full-term neonates, and the babies that are up to two months old all are detectably different from adults. The others in this first weighting scheme aren't reliably different. There is some tendency for the clearances for these age groups to be a little bit higher than adults and then to drop back down, but they're not reliably different within usual statistical criteria ($P < 0.05$).

In Table 9

**Table 9**
**Summary Regression Results Using Square Root of N Weighting**

**Dependent Variable—Log(Mean Clearance)**

**Weighting—Square Root of N**

| | |
|---|---|
| RSquare | 0.949 |
| RSquare Adj | 0.920 |
| Root Mean Square Error | 0.342 |
| Mean of Response | 0.333 |
| Observations (or Sum Wgts) | 291 |

Parameter Estimates

| Term | Antilog | Estimate | Std Error | t Ratio | Prob>\|t\| |
|---|---|---|---|---|---|
| Intercept | | -0.038 | 0.063 | -0.6 | 0.5536 |
| (Chemicals omitted) | | | | | |
| Premature Neonates | 0.25 | -0.611 | 0.108 | -5.64 | <.0001 |
| Full Term Neonates | 0.43 | -0.371 | 0.093 | -3.99 | 0.0002 |
| 1 wk- 2 months | 0.59 | -0.233 | 0.068 | -3.41 | 0.0013 |
| 2-6 months | 0.97 | -0.011 | 0.095 | -0.12 | 0.91 |
| Crawlers & Toddlers 6 mo – 2 yr | 1.49 | 0.174 | 0.091 | 1.92 | 0.06 |
| Pre-Adolescents 2-12 yr | 1.35 | 0.131 | 0.070 | 1.86 | 0.07 |
| Adolescents 12-18 yr | 0.84 | -0.075 | 0.120 | -0.62 | 0.54 |

this analysis is repeated with the square root of N weighting scheme. And in this and subsequent tables we have omitted the regression estimates for the individual chemicals--because they're not particularly important, they're just ways of normalizing the results so that we can say something about the age groups.

Now essentially what we have in Table 9 is a regression that's not so different, and we have more or less the same kind of results, with the premature neonates a quarter of the clearance of the adults, the full-term neonates 40%, one week to two months about 60%, and the rest about the same as adult (84-150%). In this analysis premature through 1 week- two months showed statistically significant differences from adults. While the others were not significant the 6 mo–2 yr and preadolescents were just short of being significantly greater than the adults at P = 0.06 and P = 0.07 respectively.

Table 10

**Table 10**
**Summary Regression Results Using Inverse Standard Error Variance Weighting**

**Dependent Variable—Log(Mean Clearance)**

**Weighting—Inverse Standard Error Variance**

| | |
|---|---|
| RSquare | 0.983 |
| RSquare Adj | 0.973 |
| Root Mean Square Error | 1.455 |
| Mean of Response | 0.467 |
| Observations (or Sum Wgts) | 27236 |

Parameter Estimates

| Term | Antilog | Estimate | Std Error | t Ratio | Prob>\|t\| |
|---|---|---|---|---|---|
| Intercept | | -0.045 | 0.036 | -1.23 | 0.22 |
| (Chemicals omitted) | | | | | |
| Premature Neonates | 0.29 | -0.530 | 0.120 | -4.43 | <.0001 |
| Full Term Neonates | 0.62 | -0.211 | 0.046 | -4.53 | <.0001 |
| 1 wk- 2 months | 0.73 | -0.136 | 0.043 | -3.17 | 0.0027 |
| 2-6 months | 1.14 | 0.056 | 0.061 | 0.92 | 0.36 |
| Crawlers & Toddlers 6 mo – 2 yr | 1.55 | 0.190 | 0.065 | 2.9 | 0.0056 |
| Pre-Adolescents 2-12 yr | 1.33 | 0.125 | 0.042 | 3.02 | 0.0041 |
| Adolescents 12-18 yr | 0.88 | -0.055 | 0.096 | -0.57 | 0.57 |

illustrates the same regression analysis using inverse standard error variance weighting. And this actually performs quite a bit better as it turns out, with an appreciably higher $R^2$ and greater capabilities to detect differences that are highly significant statistically. What this is telling us is that this weighting system is downgrading some of the points that are actually really more variable, or really more uncertain than we were counting earlier. The effect size is a little bit less, so now we've got the premature neonates up to 29% of the adult values—however this is not reliably different than what we had before. The full-term neonates are about 60% of the adult values in this clearance function. The one-week to two-months about 73%. But because of the increased power of the regression that has a pretty decent P value.

The two-to-six-months babies are very similar to adults, but now we have a distinct tendency to go a little higher in clearance for some of the other young-kid age groups (toddlers and preadolescents $P < 0.01$) and then clearance falls back toward the adult value by adolescence.

We think what this pattern is probably telling us is that because clearance is weight-normalized, the right normalization is probably something like body weight to the three-quarters or something like that. Very early in infancy it is likely that there is some real maturation of clearance functions, but once the full adult clearance has developed, normalization by body weight to the three-quarters will probably reveal more consistency with adult values across the child/adolescent age groups.

Those are the basic results for the clearance parameter. Table 11

**Table 11**
**Summary Regression Results Using Inverse Standard Error Variance Weighting**

**Dependent Variable—Log(Elimination Half Life)**

**Weighting— Inverse Standard Error Variance**

| | |
|---|---|
| RSquare | 0.984 |
| RSquare Adj | 0.975 |
| Root Mean Square Error | 2.514 |
| Mean of Response | -0.172 |
| Observations (or Sum Wgts) | 39462 |

| Parameter Estimates Term | Antilog | Estimate | Std Error | t Ratio | Prob>\|t\| |
|---|---|---|---|---|---|
| Intercept | | 0.885 | 0.041 | 21.84 | <.0001 |
| (Chemicals omitted) | | | | | |
| Premature Neonates | 3.91 | 0.592 | 0.141 | 4.19 | <.0001 |
| Full Term Neonates | 2.05 | 0.313 | 0.072 | 4.36 | <.0001 |
| 1 wk- 2 months | 1.88 | 0.275 | 0.051 | 5.38 | <.0001 |
| 2-6 months | 1.17 | 0.067 | 0.066 | 1.02 | 0.31 |
| Crawlers & Toddlers 6 mo – 2 yr | 0.86 | -0.065 | 0.088 | -0.74 | 0.46 |
| Pre-Adolescents 2-12 yr | 0.98 | -0.008 | 0.046 | -0.18 | 0.86 |
| Adolescents 12-18 yr | 1.06 | 0.027 | 0.169 | 0.16 | 0.87 |

shows similar findings with the same, more sophisticated weighting, inverse standard error variance, for elimination half-lives. These results show a qualitatively similar picture, but now of course we have positive numbers for the log estimates for the youngest age groups—the decreased clearance is associated with longer elimination half-lives. So premature neonates, for example, have about four times the half-life of, on average, compared to adults. Similarly the full-term neonates have about twice the half-life on average, as adults, as does the next category. And these are all pretty solidly different in statistical terms from the adults ($P < 0.0001$). Moving on to the next older

age categories, we don't have too much going on below the line here. We're basically getting adult values beyond this point, from 2-6 months of age. Table 12

**Table 12**
**Summary Regression Results Using Inverse Standard Error Variance Weighting**

**Dependent Variable—Log(Volume of Distribution)**

**Weighting— Inverse Standard Error Variance**

| | |
|---|---|
| RSquare | 0.933 |
| RSquare Adj | 0.889 |
| Root Mean Square Error | 1.780 |
| Mean of Response | -0.256 |
| Observations (or Sum Wgts) | 15421 |

Parameter Estimates

| Term | Antilog | Estimate | Std Error | t Ratio | Prob>\|t\| |
|---|---|---|---|---|---|
| Intercept | | -0.378 | 0.033 | -11.52 | <.0001 |
| (Chemicals omitted) | | | | | |
| Premature Neonates | 1.84 | 0.265 | 0.115 | 2.29 | 0.0276 |
| Full Term Neonates | 1.09 | 0.038 | 0.111 | 0.34 | 0.74 |
| 1 wk- 2 months | 1.46 | 0.166 | 0.073 | 2.28 | 0.02 |
| 2-6 months | 1.27 | 0.102 | 0.089 | 1.15 | 0.26 |
| Crawlers & Toddlers 6 mo – 2 yr | 1.38 | 0.138 | 0.088 | 1.58 | 0.12 |
| Pre-Adolescents 2-12 yr | 1.07 | 0.029 | 0.044 | 0.65 | 0.52 |
| Adolescents 12-18 yr | 0.94 | -0.027 | 0.187 | -0.14 | 0.89 |

shows similar results for volume of distribution. This parameter does not show as dramatic a range of changes for the various age groups vs. adults. Certainly there is some difference for the premature neonates and possibly some of the younger children (1 wk – 2 mo), although this category didn't come out statistically significant. But, otherwise, we're pretty close to adult values by the time we get to the six-months of age point. Now in Table 13

**Table 13**
**Summary Regression Results for Elimination Half Lives for Chemical Subsets by Mode of Elimination**

**Any P450:**

| Term | Antilog | Estimate | Std Error | t Ratio | Prob>\|t\| |
|---|---|---|---|---|---|
| Premature Neona | 4.40 | 0.644 | 0.211 | 3.04 | 0.0051 |
| Full Term Neona | 2.27 | 0.356 | 0.110 | 3.22 | 0.0033 |
| 1 wk- 2 months | 2.12 | 0.326 | 0.076 | 4.26 | 0.0002 |
| 2-6 months | 1.35 | 0.129 | 0.099 | 1.31 | 0.20 |
| Crawlers & Todd | 0.59 | -0.232 | 0.182 | -1.28 | 0.21 |
| Pre-Adolescents | 1.19 | 0.074 | 0.079 | 0.94 | 0.36 |
| Adolescents (12 | 1.41 | 0.148 | 0.682 | 0.22 | 0.83 |

**Glucuronidation and/or Sulfation:**

| Term | Antilog | Estimate | Std Error | t Ratio | Prob>\|t\| |
|---|---|---|---|---|---|
| Premature Neona | 3.50 | 0.544 | 0.119 | 4.58 | 0.0026 |
| Full Term Neona | 2.19 | 0.341 | 0.074 | 4.61 | 0.0025 |
| 1 wk- 2 months | 1.71 | 0.234 | 0.218 | 1.07 | 0.32 |
| 2-6 months | 0.79 | -0.104 | 0.148 | -0.71 | 0.50 |
| Crawlers & Todd | 1.35 | 0.130 | 0.195 | 0.67 | 0.53 |
| Pre-Adolescents | 1.55 | 0.190 | 0.100 | 1.89 | 0.10 |
| Adolescents (12 | 1.66 | 0.221 | 0.137 | 1.62 | 0.15 |

**Renal Elimination:**

| Term | Antilog | Estimate | Std Error | t Ratio | Prob>\|t\| |
|---|---|---|---|---|---|
| Premature Neona | | | No data | | |
| Full Term Neona | 2.79 | 0.446 | 0.291 | 1.54 | 0.14 |
| 1 wk- 2 months | 2.76 | 0.441 | 0.177 | 2.49 | 0.025 |
| 2-6 months | 1.19 | 0.075 | 0.133 | 0.56 | 0.58 |
| Crawlers & Todd | 0.86 | -0.064 | 0.129 | -0.5 | 0.62 |
| Pre-Adolescents | 0.67 | -0.172 | 0.084 | -2.04 | 0.059 |
| Adolescents (12 | | | No data | | |

is an early result of what happens when we break it down by clearance categories. The modes of elimination are any P450, glucuronidation or sulfation, and renal elimination. We don't have data for the premature neonates and adolescents for the renal elimination category.

Overall this particular breakdown so far has not given us a great deal to write home about. For elimination half-lives we have the same fourfold difference approximately for the premature neonates and twofold differences for the next couple of categories, and then normalizing to pretty much adult levels later on.

Now we can turn to the issue of how much the chemicals seem to differ among themselves. This is shown in Figure 1. This graph gives the residuals from the regression controlling for the chemical-to-chemical differences but not the differences among the age groups so that you can see them more clearly. These are probability plots of the results sorted by each age group. In a probability plot essentially what you're plotting here on the ordinate, is the log, T1/2 residual, so the intercepts of the regression lines are analogous to those regression estimates, but now we are showing the results for the

individual data points relative to what they would be expected to be had they been adults. On the abscissa is the Z-score. If each of these distributions of residuals were normal, that is if the log residuals were normally distributed, you would expect to see the points lining up on the straight regression lines. As mentioned earlier, the intercept of each of those straight lines is an estimate of the central value, the median value of the residual, like the multiple regression estimate for each age group and the slope tells you how different the chemicals are in log terms. A systematic pattern of departure of the points from the straight line tells you that things are really not quite normally distributed.

So the data are more or less normally distributed. But unfortunately, if you look first at the premature neonates (Figure 1) you see four points. One can't really tell much from four points and they're not too different from each other with a log slope of 0.1 That's not very different from what you typically get for interindividual variability in pharmacokinetic parameters.

Where you see a lot more variability (full term neonates, 1 wk-2 mo infants), this tells you that the chemicals are more spread out than they are later on. And what that's telling you is that there may be more difference among chemicals for these intermediate age groups –that is, the full-term neonates and the one-week to two-months age groups. Moreover, if you look carefully at the pattern of these points for the line, we really start to get distressed, particularly for the pattern created by these squares (1 wk- 2 mo), because that's really not behaving as if it's normally distributed at all. This is distressing because we normally like to show these things with being perfectly lined up. It's really simple for an analyst if, after everything is converted to logarithms, the world is normal. This means that after you make the transformation you can predict percentiles out to where ever. But, if it's not normal then you have to come up with some other kind of explanation. And our tentative idea to understand this is that, in this early period that there are more relatively sharp transitions in time as different functions mature. And that some of the chemicals are shifting to their more adult pattern early in the period that

we've defined for these categories, and some later. Therefore, these really are likely to be mixtures of two log-normal distributions, or even bimodal distributions some of the times as some of the elimination functions have matured early, some in the middle of the defined age group category, and some later on. And we think we are seeing that pattern, as well in some of the individual deviation data that will be discussed later.

Finally in Figure 1 when we get to the age groups that are closer to adult, values are a little bit less dispersed and a little bit closer to normal distributions, despite the fact that there may be some additional odd behavior in the data showing up among the teens/adults. It could well be that there's also some mixture or bimodality going on in this teens and adults category.

Figure 2

(overhead 19)

shows the interindividual variability that can be seen for half-lives within one particular chemical. This particular chemical is valproic acid, plotted for three different age groups. The solid squares that look like they line up pretty nicely to a lognormal line are for the adolescents and adults. The four- to eight-year-olds have a rather small amount of variability. The four-to-eight-year-olds have a much more normal amount of interindividual variability and something that's not completely conforming to the straight line but it's closer. However the open squares which represent the youngest age group of 0.25 to two-year-olds really does have a suspicious-looking bend to it. And we think the likely explanation is that some of these young kids have, again, undergone a sharp transition to the fully adult state of the elimination. And so this probably needs to be interpreted as a mixture of two log normals or some other distribution rather than a simple unimodal distribution.

Figure 3

(overhead 20)

is another similar kind of case that kind of goes a little bit in the other direction. These are now clearance data, combined from two different studies, McRorie et al. (1992) and Pokela et al. (1993), which look more or less similar when you plot them together. The filled circles are the neonates less than one week old, and that's a pretty decent log normal distribution. The filled squares are the one week to two months neonates and we are less happy with that in that there is more departure from the straight line or log normality. The filled triangles are the two months to six months infants and this really starts to look like it's got a couple of humps in it, and the same thing with the six-month to two and a half years. We are therefore really not too happy with the fit of the log normal distribution to these data sets.

So that when we're getting into these narrowly-defined age groups we're starting to find that our usual assumption that the world is log normal is not accurate, it may not be good enough, and may be telling us that we should be asking for different kinds of information, that we're suggesting some kind of sharp transitions that happen to some kids earlier than others and create this kind of irritating pattern.

The world can be complicated, we weren't consulted in its design, but the Designer showed no notable reluctance to introduce a little complexity. Given that, we just have to appreciate it, and represent it the best we can in our risk assessment modeling.

With modern computers and a lot of data we can describe mixed distributions. The difficulty statistically is you need a lot more data to calibrate a mixed distribution. For illustration, if you have only one mode in a distribution you can achieve a complete description with a mean and a standard deviation in log space that's two parameters. But if you think you have essentially a mixture of two distributions then you need at least five parameters. You need two means, two standard deviations and a proportion of the people that go in each subpopulation. So that already becomes a great deal more complicated statistical model, one that will no doubt able to describe the data, but you

have to worry about whether you've got enough degrees of freedom with the limited data set to really sort it out reliably.

The other source of information is these ICRP (1995) radionuclide dose coefficients that I think can tell us something about what's happening. These dose coefficients are the combined result of the operation of a respiratory deposition model, a clearance model, a dosimetric model; they don't have a variability model, so they don't tell us how variable they think the population is in these doses, but there's at least another source of somebody's careful estimates of how different age groups of kids are. The database is constructed from height and weight data from NHANES II, the previous NHANES survey, airway dimensions from linear height regressions, anatomical dead space from exponential height regressions, and other quantitative relationships derived empirically from basic data. For example, they've got ventilation rate calculated from basal metabolic rate activity patterns, tidal volumes calculated from a linear age relationship and a linear height relationship.

And then they've got a dosimetry model- how much radiation should be expected to be absorbed in different organs, depending on the geometry of the organ mass (from exponential age distributions and some absorption rate assumptions}.

Anyhow for these different ages of children the ICRP results can be used to derive child-to-adult ratios of predicted dose where the units here are Sieverts (Sv)-per-Becquerel (Bq)

(Overhead 22)

.It can be seen that there are a number of examples of substantial child/adult dose ratios. For example for strontium we've got ratios up to as much as fivefold, for the three-month-old declining toward the adult level for the older children. For cesium 136 we have a fairly similar pattern but there is A less extreme pattern for cesium 134. And for plutonium we have essentially very little differences across age groups. It clearly matters for these projections where the chemical goes and how quickly.

I should say, in conclusion, that anybody who wants this database, you're free to have it. We expect to make it available on our website in the form of Excel files, and it can be made available sooner on request for any agency or other researcher who has a use for it.

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